Alterations of Bile Acids and Gut Microbiota in Obesity Induced by High Fat Diet in Rat Model

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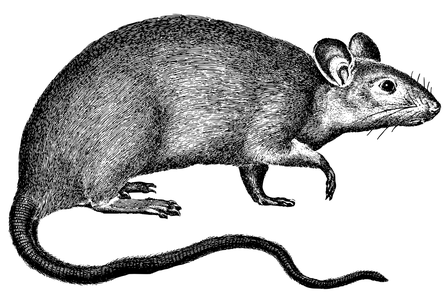
INTRODUCTION

An increasing number of evidence has illustrated that obesity is a metabolic disease and characterized as low-grade chronic inflammation, which was caused by excess nutrient uptake and insufficient energy expenditure[1,2,3,4,5]. Obesity is one of the important risk factors for other metabolic diseases, such as insulin resistance, type 2 diabetes, etc.[4,6,7]. Our previous research has reported that the development of obesity was accompanied by the alteration of gut microbiome and fecal metabolites[21,22]. In the present research, we aim to investigate the impact of high-fat diet induced changes in rat model with emphasis on the interplay between bile acids and gut microbiota. We first of all optimized the UPLC-MS technique for bile acids quantification and then investigated dynamic changes of bile acids and gut microbiota in response to a high-fat diet. We comprehensively monitored bile acids from their generation to circulation and reabsorption in rats fed a high-fat diet. Our work provided details of the “life-cycle” of bile acids and their modulation by the gut microbiome during the progress of obesity. In addition, our work revealed the potential function of a specific strain of microbiota on bile acid modulation.

MATERIALS AND METHODS



This study utilized male Sprague-Dawley rats (n=24), which were randomly divided into two groups: one fed a normal diet (control group) and the other fed a high-fat diet (HFD group) for 81 days. Feces, plasma, liver, and segments of intestinal tissues (jejunum, ileum, cecum, and colon) were collected at specific intervals. Plasma was prepared with sodium heparin as an anticoagulant, while tissues and fecal samples were snap-frozen in liquid nitrogen and stored at −80°C until analysis. Bile acids were extracted and quantified using ultraperformance liquid chromatography coupled with mass spectrometry (UPLC-MS), ensuring high sensitivity and throughput. Gut microbiota composition and bile acid correlations were analyzed using previously published microbiota data. Statistical comparisons were performed using Student’s t-test or Kruskal-Wallis tests for non-normal data, and heatmaps of correlations between bile acids and microbiota were generated using MATLAB and R software.

RESULTS AND CHARTS

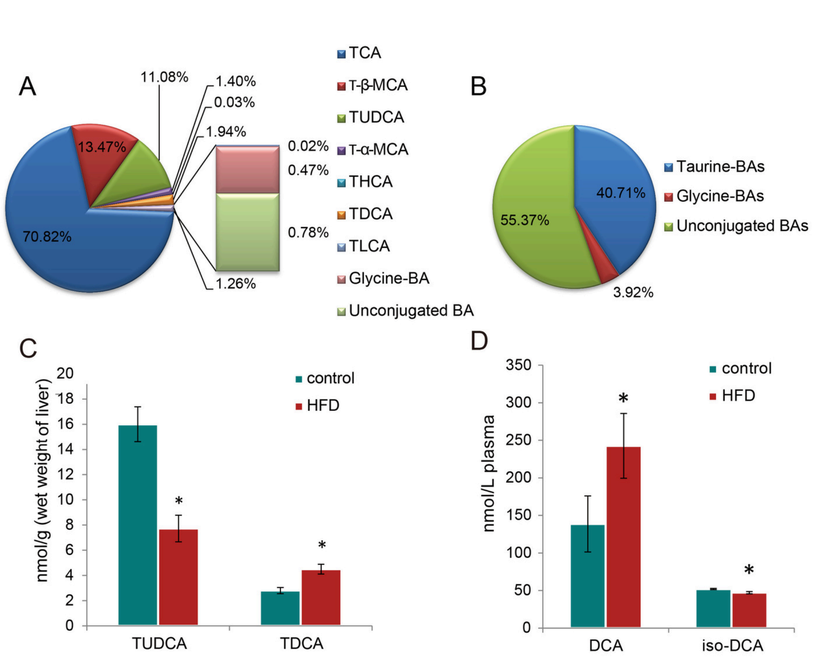


Fig. 1. Bile acid compositions in (A) liver and (B) serum from rats fed with normal diet for 81 days. (C) Concentrations of TUDCA and TDCA in liver from control and HFD groups. (D) Concentrations of DCA and iso-DCA in plasma from control and HFD groups. Data are collected with UPLC-MS/MS method and own as mean ± SEM in histograms (C) and (D).

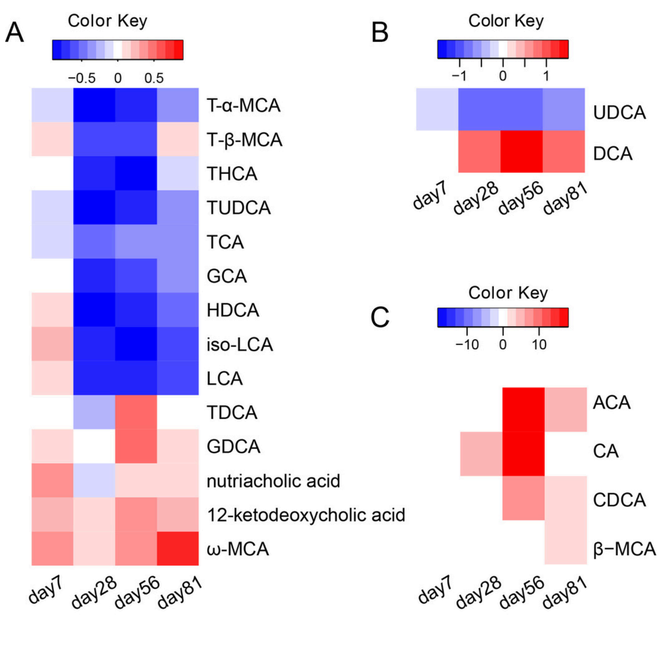


Fig.4 Heat map showing the relative variations of fecal bile acids, represented as (CHFD− CControl)/CControl at days 7, 28, 56, and 81 compared HFD group with control group (n = 12). Relative variation ratios are within range (A) from−1 to 1; (B) from−1.5 to 1.5; and (C) from−15 to 15.

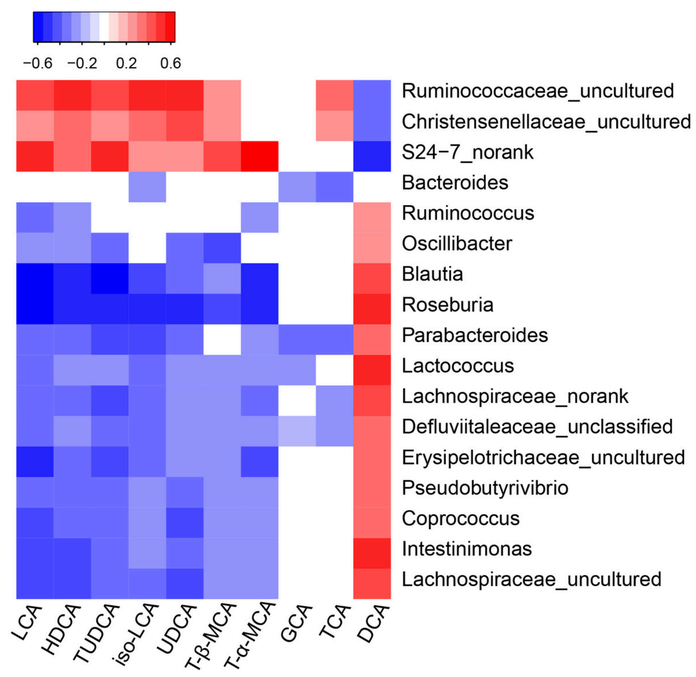


Fig. 5 Heat map showing Pearson’ correlation coefficient with p <0.05 betwee several significant changed fecal bile acids and general bacteria. Red cells represent positive correlation and blue cells represent negative correlation.

DISCUSSION AND CONCLUSION

The study revealed significant alterations in bile acid profiles and gut microbiota composition due to a high-fat diet (HFD). HFD-fed rats exhibited increased levels of deoxycholic acid (DCA) and taurodeoxycholic acid (TDCA) across the enterohepatic system, while levels of ursodeoxycholic acid (UDCA) decreased. Fecal bile acids showed dynamic shifts, with a reduction in conjugated bile acids such as TUDCA and GCA, and an increase in unconjugated bile acids like DCA. Correlation analysis linked higher DCA levels to bacterial genera such as Blautia, Coprococcus, and Ruminococcus, while conjugated bile acids were negatively associated with Lachnospiraceae and other bacterial taxa. The findings highlight the role of HFD in disrupting the balance of bile acids and gut microbiota, which may exacerbate obesity-related health risks. Elevated DCA levels, known for their hydrophobic nature, can impair intestinal barrier integrity and contribute to DNA damage [14,36,37]. Conversely, the increased total bile acid pool may reflect a compensatory metabolic response, potentially activating pathways like TGR5 and FXR to mitigate obesity's effects [8,41,42,43]. The reduction in fecal conjugated bile acids underscores the role of gut bacteria in bile acid deconjugation. This study provides a comprehensive view of the interactions between diet, gut microbiota, and bile acids, offering insights into potential therapeutic targets for obesity-related metabolic disorders. In conclusion, the present study demonstrated the alterations of bile acids and gut microbiota in a high fat diet induced obese in rat model, particularly the levels of DCA in enterohepatic circulation and in feces. The correlations between fecal bile acids and intestinal microbiota offered important clues to exploring specific strains involved in bile salt hydrolases and 7-α-dehydroxylation. These findings allowed us to realize the roles of bile acids and gut microbiota in the development of obesity, providing a novel view for under- standing the obesity-related metabolic diseases.

ACKNOWLEDGEMENTS AND BIBLIOGRAPHY

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